Antibiotic Treatment Against Methicillin-Resistant
Staphylococcus aureus Hospital- and Ventilator-acquired Pneumonia: A Step Forward but the Battle Continues

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(See the Major Article by Wunderink et al, on pages 621–9.)

Methicillin-resistant Staphylococcus aureus (MRSA) is the second most frequent microorganism-based cause of hospital-acquired (HAP) and ventilator-acquired pneumonia (VAP) [1]. However, its frequency in the ranking of microorganisms causing HAP and VAP varies greatly between countries and departments [2]. MRSA HAP and VAP are associated with a high health cost, morbidity, and mortality (between 40% and 60%) [3]. For many years, the standard antibiotic treatment available against these formidable respiratory infections has been glycopeptides such as teicoplanin and, principally, vancomycin. It has been known for a long time that vancomycin has poor penetration in the lung and the potential side effects are mainly due to its renal toxicity [4–6]. The use of these glycopeptides as the main weapon against HAP and VAP caused by MRSA has been viewed as suboptimal by experts and clinicians, with rates of clinical failure ranging from 60% to 70%. In the last 10 years, the pharmaceutical industry has made efforts to develop antibiotics against gram-positive cocci, including MRSA. Linezolid, a member of the oxazolidinone family, is an antibiotic that has been used for more than 10 years to combat staphylococcal infections.

In randomized clinical trials (RCTs), linezolid has been compared with vancomycin (the “gold standard”) in HAP and VAP S. aureus infections without showing differences in clinical cure in studies designed for noninferiority [7, 8]. The pooled post hoc analyses focusing on gram-positive infections [9, 10] performed after these trials showed significant advantages in favor of linezolid for both clinical cures and mortality. These post hoc analyses were criticized because of their retrospective nature and for the following reasons inherent to the design of the initial trials [7, 8]: (1) dosages of vancomycin were not adjusted according to the trough values, which meant that part of the patients treated could have been underdosaged; (2) minimal inhibitory concentration (MIC) values of MRSA for vancomycin were not taken into account; (3) methicillin-susceptible S. aureus (MSSA) and MRSA, HAP, and VAP were included in the same trials; and (4) the impact of dual (gram-positive plus Gram-negative) infections was not clarified. Furthermore, 2 meta-analyses comparing glycopeptides with linezolid in HAP/VAP MSSA and MRSA found no clinical or microbiological differences [11, 12] between the 2 treatments. In one study [11], renal adverse events were not higher when using vancomycin. By contrast, they found higher rates of leucopenia and diarrhea with linezolid. However, these meta-analyses were not exempt from pitfalls as commented by Luna et al [13]. These pitfalls were again related to the design of the trials included.

In this issue of Clinical Infectious Diseases, Wunderink et al [14] show the results of the first RCT comparing linezolid with vancomycin, exclusively focusing on MRSA respiratory infections. They included HAP and VAP and approximately 15% of healthcare-associated pneumonia (HCAP) patients. In the pre-protocol and modified intent-to-treat populations, they found a significantly better clinical cure with linezolid (58%) compared with vancomycin (47%). These results were also favorable for linezolid in terms of microbiological cure (58% vs 47%). However, there was no difference in mortality at 60 days between the 2 arms.

This study has merits and that is why this editorial is entitled “A Step Forward.” First, this study is the first RCT that
exclusively included patients with MRSA hospital-acquired respiratory infections. Second, in this trial, vancomycin was studied in optimal conditions for comparison with linezolid: dosages were locally adjusted according to trough levels and renal function; MICs of MRSA isolates for vancomycin were monitored; treatments with linezolid or vancomycin within 72 hours before the study period were excluded, thereby avoiding the inclusion of patients with early failure; and, finally, treatments were prolonged to 21 days in case of bacteremia, thereby avoiding bias when analyzing recurrence or persistence in blood. Despite all of these optimal conditions for vancomycin, clinical and microbiological cures were significantly better for linezolid.

As with any RCT, there are some aspects that merit comment:

1. According to the European view on HCAP [15], the inclusion of HCAP patients adds heterogeneity to the overall population studied. However, these patients represented only 15% of the total population.

2. When the populations are broken down into the 3 types of patients included (HCAP, HAP, and VAP), significance was lost. However, the numerical trends in favor of linezolid are maintained. The authors do not show the results of pooling together HAP and VAP patients.

3. Mixed Gram-negative and MRSA infections were also included, and the issue of inadequate anti-Gram-negative treatment might be raised. However, according to design of the study, all Gram-negative patients received adequate initial treatment.

4. The 60-day mortality rate (and, I imagine, the 28-day mortality rate, according to the survival curves shown in Figure 3 in the “Appendix”) was the same. However, this was a noninferiority trial for clinical cure and did not have the capacity to study differences in mortality.

An important point of the study in favor of linezolid are the rates of renal adverse effects (recorded in the study as renal failure/impaired/azotemia), which were twice as high in the vancomycin arm (7.3% vs 3.7%) as in the linezolid arm. Renal failure is a clear risk factor for mortality in HAP and VAP patients. The authors do not report the mortality of the population that developed renal insufficiency, which I assume is very high. The risk of developing renal failure with vancomycin is well documented in the literature [4–6]. Recent information suggests that this risk is increased with higher trough levels of vancomycin [16] with rising dosages and when there is an impaired baseline renal function [17].

Models of MRSA in ventilated pigs have provided important additional information. Luna et al [18] found lower histopathological severity of pneumonia in piglets treated with linezolid compared with glycopeptides. In a recent manuscript from our group in a similar model, Martinez et al [19] found less systemic inflammation, lower histopathological severity of pneumonia, and lower lung bacterial load. Moreover, pharmacokinetic/pharmacodynamic (PK/PD) indices were better with linezolid.

The recommendations of the latest Infectious Diseases Society of America and American Thoracic Society guidelines on linezolid and vancomycin placed these 2 antibiotics at similar a level [20]. In these recommendations, linezolid was preferred in case of baseline renal failure or in nonresponding patients. Now, with all of the information that we have in our possession, the recommendations regarding linezolid must be reconsidered and probably expanded. In addition to the better clinical and microbiological cures observed in this study, the risk of renal failure with vancomycin is a strong argument in favor of linezolid. In addition, many HAP and VAP patients may receive aminoglycosides for empirical or definitive treatment, and this may increase the risk of developing renal failure [6]. Finally, clinical failure [21] and mortality of MRSA seem to be increased in patients with vancomycin MICs ≥2 mg/L. The MRSA MIC creep for vancomycin (33 out of 174 cases in the study in question) is a well-described phenomenon and is an important concern in some countries [21].

In contrast, we cannot disregard the cost of the antibiotic and potential appearance of outbreaks of MRSA resistant to linezolid as it has been recently described in JAMA by Sanchez et al [22]. Bearing this in mind, we must make an effort to administer linezolid in clinically and microbiologically well-documented cases of HAP and VAP MRSA infection.

In conclusion, and although I think that vancomycin still has a role to play in the treatment of MRSA HAPs, animal and human studies suggest PK/PD, microbiological, and clinical advantages of linezolid in comparison with vancomycin for the treatment of hospital-acquired MRSA respiratory infections. However, the percentages of clinical cure are still far from optimal—the battle continues.

Notes

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References


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